

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 9/24, 9/52, 31/44</p>	<p>A1</p>	<p>(11) International Publication Number: WO 95/01783 (43) International Publication Date: 19 January 1995 (19.01.95)</p>
<p>(21) International Application Number: PCT/SE94/00681 (22) International Filing Date: 8 July 1994 (08.07.94) (30) Priority Data: 9302395-0 9 July 1993 (09.07.93) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BENGTTSSON, Inga, Siv [SE/SE]; Klintens väg 13, S-414 76 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: LARSSON, Birgitta; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published With international search report.</p>
<p>(54) Title: NEW PHARMACEUTICAL FORMULATION (57) Abstract A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

NEW PHARMACEUTICAL FORMULATION

5 Field of the invention

The present invention is related to a new pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, to a method for the manufacture of such a formulation, and to the use of such a formulation in
10 medicine.

Background of the invention

The compound known under the generic name omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is described
15 i.a. in EP-A 0 005 129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity. In a more general sense, omeprazole may be used for
20 prevention and treatment of gastric acid related disorders in mammals and man, including e.g. gastroesophageal reflux disease, gastritis, gastric ulcer and duodenal ulcer. Omeprazole is susceptible to degradation/transformation in acid reacting and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values
25 degradation proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). Omeprazole also in the solid state is susceptible to degradation and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also
30 affected by moisture, heat, organic solvents and to some degree by light.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid
5 absorption of omeprazole can occur.

A pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating. In US-A 4,786,505 is described an enteric coated omeprazole preparation containing a separating subcoat
10 between the core material and the enteric coating. Said preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating.

Certain salts of omeprazole including alkaline reacting salts of omeprazole are described in EP-A 0 124 495. In said patent specification the requirements and
15 importance regarding storage stability of omeprazole for incorporation in pharmaceutical preparations are emphasized.

There is however, a demand for the development of new enteric preparations of omeprazole with enhanced stability and for environmental aspects there is also a
20 strong desire for the use of water based processes in production of pharmaceutical products.

The isolation and purification in full manufacturing scale of the magnesium omeprazole salts described in EP-A 0 124 495 presents one major problem in that
25 the magnesium omeprazole salt particles are very fragile making pharmaceutical manufacturing processes utilising this product less attractive in full scale production. Performing the process without crystallization of the magnesium omeprazole gives a product which is less suitable as a pharmaceutical substance.

30 In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that

said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible.

5 The combination of physical properties of the novel magnesium omeprazole product described in the present specification with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, low water content and low content of other solvents is favorable and permits the manufacture of magnesium omeprazole in a form which is useful for the manufacture of the new pharmaceutical formulation.

10

The novel form of magnesium omeprazole can be formulated into different dosage forms for oral and rectal administration. Examples of such formulations are tablets, granules, pellets, capsules, suppositories and suspensions.

15 Description of the invention

One object of the present invention is to provide a pharmaceutical formulation of magnesium omeprazole.

20 Another object of the present invention is to provide a process for full scale production of pharmaceutical formulations of omeprazole, especially an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and has a good stability during long-term storage.

25

Yet another object of the invention is to provide an environmental friendly completely water-based process for the manufacture of pharmaceutical formulations of omeprazole.

30 The new dosage form is characterized in the following way. Core material in the form of pellets, granules or tablets containing the novel form of a magnesium salt of omeprazole, optionally together with an alkaline reacting compound, and on said

core material one or more subcoating layers optionally comprising tablet excipients which are soluble or insoluble but disintegrating in water, or polymeric, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the core and an outer layer, which is an enteric coating. This/these inner layer/layers separates/separate the core material from the outer layer being an enteric coating.

The process of forming the enteric coated dosage form is preferably water-based. Also the enteric coating process step, which usually is carried out using an organic solvent, can be carried out using a water-based process which is desirable both for the working environment inside the pharmaceutical plant and for global environmental reasons.

It has been found that a magnesium omeprazole having a degree of crystallinity which is higher than 70% is useful in the manufacture of the pharmaceutical formulations of omeprazole according to the present invention.

Detailed description of the invention

The new pharmaceutical formulation is defined in claims 1-8, a process for the manufacture of the pharmaceutical formulation according to the present invention is defined in claims 9-10 and the use of the formulation in medicine is defined in claims 11-17.

Magnesium omeprazole

Magnesium omeprazole feasible for the manufacturing of the claimed formulation has the following properties:

- a) Crystalline form, with a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

It is desirable that the product also exhibits the following properties;

- 5 b) Particle size measured as mean mass diameter (MMD) less than 30 μm , preferably less than 20 μm as determined by laser diffraction technique.
- c) Density between 1.33 g/cm^3 and 1.35 g/cm^3 as determined by powder pycnometer.
- 10 d) Hygroscopicity not exceeding 2% increase of weight upon storage for one month up to 94% relative atmospheric humidity as determined gravimetrically.
- e) A content of water of between 5% and 10% by weight as determined by 15 titration according to Karl Fischer.
- f) A content of methanol less than 0.1% preferably less than 0.05% by weight as determined by gas chromatography, in case methanol is used as solvent.
- 20 The process for producing the novel form of magnesium omeprazole is characterized by the following consecutive steps
- 1) treating omeprazole or a salt thereof with magnesium alcoholate in a solution
- 25 2) separating inorganic salts from the reaction mixture
- 3) crystallizing magnesium omeprazole
- 4) isolating the obtained crystalline magnesium omeprazole and, optionally 30
- 5) purifying and drying the crystalline magnesium omeprazole using conventional methods.

The process for manufacturing the novel magnesium omeprazole can be described in the following way:

A lower alcohol, such as methanol, ethanol, n-propanol or iso-propanol, preferably methanol, is treated in a solution of polar solvents with a weighed amount of magnesium at temperatures between 0°C and reflux temperature. The temperature should preferably be between 10 and 30°C. After addition of the magnesium to the solution the temperature can, in a second step be raised further to between 0°C and reflux temperature, preferably 20-50°C. After termination of the reaction the temperature is reduced to 0-40°C, preferably 10-25°C. Omeprazole or a salt of omeprazole is then added to the solution and after termination of the reaction the mixture is cooled to -10°C to +20°C, preferably -5°C to +5°C. The solvent is then evaporated to 40-60% of the initial volume, which makes the inorganic salts precipitate. The precipitate is separated from the reaction solution for example by centrifugation or filtration and the solution is heated to 5°C to 30°C whereafter the solution is seeded with magnesium omeprazole crystals. An amount of water, which is approximately equal to the volume of the solution, is added to start the crystallization. The solution is cooled to -10 to +20°C, preferably 0-10°C to complete the crystallization. The crystals are then separated from the mother liquid for example by centrifugation or filtration and washed with polar solvents preferably an aqueous lower alcohol such as aqueous methanol. Finally, the crystals are dried preferably under reduced pressure and heating.

Pharmaceutical formulations containing the novel magnesium omeprazole described above are manufactured as described herein below.

Core material

The novel magnesium salt of omeprazole, herein referred to as magnesium omeprazole, is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture. Optionally the magnesium omeprazole may be mixed with an

alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

The powder mixture is then formulated into pellets, granules or tablets, by conventional pharmaceutical procedures. The pellets, granules or tablets are used as core material for further processing.

Separating layer - subcoating.

The cores containing magnesium omeprazole and optionally alkaline reacting substances are separated from the enteric coating polymer(s). The subcoating layer, in the following defined as the separating layer, serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the core can react with hydroxyl ions diffusing from the core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and

aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids or salts thereof.

- 5 The separating layer may consist of one or more layers.

The separating layer(s) can be applied to the core material - pellets, granules or tablets - by conventional coating procedures in a suitable coating pan, centrifugal fluidized coating-granulator, or in a fluidized bed apparatus using water and/or
10 conventional organic solvents for the coating solution. The material for the separating layer is chosen among pharmaceutically acceptable, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxymethyl cellulose or
15 hydroxypropyl methylcellulose. The separating layer, "subcoating", applied to the core material may constitute from approximately 0.5 to 25 % by weight of the core weight, preferably 2.0 - 10.0 %, and more preferably 2.5 - 5.0 %.

In the case of a tablet formulation another method to apply the separating layer(s)
20 can be performed by drycoating technique. First a tablet containing magnesium omeprazole is formulated as described above. Around this tablet one or more layers are compressed using a suitable tableting machine. The separating layer(s) consists of pharmaceutically acceptable, soluble or insoluble but in water disintegrating
tablet excipients. The separating layer(s) has preferably a thickness of not less than
25 approximately 1 mm.

Ordinary plasticizers, colorants, pigments, titanium dioxide, talc and other additives may also be included into one or more of the separating layer(s).

Enteric coating layer

- The enteric coating layer is applied in one or more layers onto the subcoated core material by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water, or by using latex suspensions of said polymers or optionally using polymer solutions in suitable organic solvents. As enteric coating polymers can be used one or more of the following, for example solutions or dispersions of acrylates (methacrylic acid/methacrylic acid methylester copolymer), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s). Preferably water-based polymer dispersions such as for example compounds known under the trade names Aquateric® (FMC Corporation), Eudragit® (Röhm Pharma), AcoatTM (Shin-Etsu Chemical), OpadryTM (Colorcon) or similar compounds are used to obtain enteric coatings. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer for example cetanol, triacetin, citric acid esters such as, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate, polyethylene glycol (PEG) or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-50 % of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer or sprayed onto the enteric coated material as an overcoat.
- The thickness of the enteric coating may vary widely without influencing the in vitro release of omeprazole in test solutions which mimic in vivo conditions in man. To protect the acid susceptible omeprazole compound and to obtain an acceptable acid resistance, the enteric coating constitutes at least an amount of 1.0 % by weight of the core weight, preferably at least 3.0 % and especially at least 6.0 %. The upper amount of the applied enteric coating is normally only limited by processing conditions. This possibility to vary the thickness of the enteric coating without deleterious influence on the release of omeprazole is

especially desirable in large scale processes. The enteric coating layer(s) may be applied on the pre-processed formulation containing subcoating layer(s) without exactly controlling the thickness of the applied coating layer(s).

5 Thus, the formulation according to the invention consists of core material containing magnesium omeprazole optionally mixed with alkaline reacting compound(s). The addition of alkaline reacting material is not necessary, in any sense, but such a substance may further enhance the stability of omeprazole. The core material is coated with an enteric coating rendering the dosage form insoluble
10 in acid media, but disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The core material is further coated with an soluble or insoluble but in water disintegrating coating, optionally containing one or more pH-buffering substances, which separate the core material from the enteric coating.

15

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets or granules, these pellets or granules dispensed in hard
20 gelatin capsules or sachets. The final dosage form may further be coated with an additional layer containing pigment(s) and/or colorant(s). It is essential for the long term stability during storage that the water content of the final dosage form containing magnesium omeprazole (enteric coated tablets, capsules, granules or pellets) is kept low.

25

Process

A process for the manufacture of a dosage form according to the present invention represents a further aspect of the invention. After the forming of the core material,
30 said material is first coated with the separating layer(s) and then with the enteric coating layer(s). The coating(s) are carried out as described above. Further another

aspect of the invention is that the pharmaceutical processes can be completely water-based.

5 The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

10 The invention is illustrated in detail by the following examples. Example 1 discloses the preparation of the novel magnesium omeprazole product, which product is suitable in manufacturing of the pharmaceutical formulations according to the present invention. Example 2 discloses compositions of different enteric coated tablets containing magnesium omeprazole and results from acid resistance
15 test and in vitro dissolution test. Examples 3 discloses tablet formulations with different thickness of the enteric coating, the obtained gastric acid resistance of said formulations and the in vitro release rate of omeprazole. Example 4 discloses an enteric coated pellet formulation.

20 Examples

The following detailed Example 1 will serve to illustrate a process for manufacturing the magnesium omeprazole, which will be used in the pharmaceutical preparations according to the present invention.

25

Example 1

A reactor was filled with 2026 litres of methanol. The stirrer was started and the temperature was adjusted to 20°C. 3,90 kg of magnesium was added to the vessel
30 and immediately thereafter 1,0 litre of CH₂Cl₂. The reactor was heated to 40°C and kept at this temperature for 60 min. It was then cooled to 15°C before the addition of 99,9 kg of omeprazole. The reactor was kept at this temperature for

60 min and then cooled to 0°C. The temperature was kept at this level for 30 minutes before 1000 L of methanol were evaporated under vacuum and the inorganic solid salt was separated from the liquid first by centrifugation and then by filtration. The liquid was heated to 10°C and the liquid was seeded with magnesium omeprazole crystals whereafter the magnesium omeprazole salt was precipitated by addition of 900 L of water. The mixture was then cooled to 5°C. After the crystallization had been completed the magnesium omeprazole crystals were centrifuged off and then washed with a mixture of 50 L of methanol and 150 L of water. The produced magnesium omeprazole was dried under reduced pressure finally producing 92,5 kg of crystalline product corresponding to a yield of 81,4%.

The novel form of the magnesium salt of omeprazole according to Example 1 fulfills the properties defined above.

Example 2

Tablet formulations containing magnesium omeprazole.

Amount omeprazole	10	20	40
Ingredient	(mg/tabl)	(mg/tabl)	(mg/tabl)

Tablet core

Magnesium omeprazole	11.2	22.5	45.0
Mannitol	68.7	57.4	34.9
Microcrystalline cellulose	25.0	25.0	25.0
Sodium starch glycolate	6.0	6.0	6.0
Hydroxypropyl methylcellulose	6.0	6.0	6.0
Talc	5.0	5.0	5.0
Sodium stearyl fumarate	2.5	2.5	2.5
Water purified	50.0	50.0	50.0

Sub-coating layer

	Hydroxypropyl methylcellulose	3.7	3.7	3.7
	Hydrogen peroxide 30%	0.04	0.04	0.04
5	Water purified	34.0	34.0	34.0

Enteric coating layer

	Methacrylic acid copolymer	9.1	9.1	9.1
10	Polyethylene glycol	1.0	1.0	1.0
	Titanium dioxide	0.82	1.1	0.51
	Colour iron oxide, red-brown	0.04	0.13	0.43
	Colour iron oxide, yellow	0.02	-	-
	Water purified	45.0	45.0	45.0

15

Polish

	Paraffin powder	0.05	0.05	0.05
--	-----------------	------	------	------

- 20 The tablets with an amount of 20 mg omeprazole/tablet have been manufactured both in a pilot scale of about 300 000 tablets and a large scale of about 2 million tablets.

Description of manufacturing

25

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are sub-coated with a polymer film based on hydroxypropyl methylcellulose and enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

30

Investigation of acid-resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

Tablet Strength (mg)	Acid resistance (%)	
10	95	(93-98)
20	100	(94-102)
40	100	(96-103)

15 Investigation of in-vitro dissolution

After exposure to acid environment, pH 1.2, as described above, the medium was switched to artificial intestinal fluid without enzymes, pH 6.8. The dissolved amount of omeprazole was determined by HPLC.

Tablet Strength (mg)	Dissolved amount of omeprazole (%) after (minutes)						
	0 (%)	5 (%)	10 (%)	15 (%)	20 (%)	25 (%)	30 (%)
10	0	2	78	92	93	94	94
20	0	0	75	93	96	96	97
40	0	9	71	86	91	91	94

All values of dissolved amount of omeprazole are mean values of 12 tablets.

Example 3

Tablet formulations containing magnesium omeprazole with different thickness of the enteric coating.

5

The composition of the tablets is the same as in Example 2 (20 mg omeprazole). The tablets (n=6) have been exposed in an artificial gastric juice (pH 1.2) during 2 hours and then analysed for remaining amount of omeprazole (acid resistance). The release of omeprazole was analysed on tablets (n=6) pre-exposed in gastric juice 2 hrs and thereafter exposed in a buffer solution (pH 6.8) during 30 min.

10

Experiment ^{x)}	Enteric coating (% weight per tablet)	Acid resistance (% residue after 2h; pH 1.2)	Release (% after 30 min; pH 6.8)
A	8	101 (98-105)	94 (93-96)
15 B	8	100 (98-102)	95 (85-98)
C	16		98 (96-100)

20 ^{x)} A manufactured in large scale
B manufactured in pilot scale
C manufactured in laboratory scale

Example 4

Enteric coated pellet formulation containing magnesium omeprazole.

25

Pellet core

	Magnesium omeprazole	225 g
	Mannitol	1425 g
30	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g

		16
	Lactose anhydrous	80 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate dihydrate	8 g
5	Water purified	350 g

Subcoating layer (I)

	Hydroxypropyl methylcellulose	70 g
10	Water purified	1450 g

Enteric-coating layer (II)

	Methacrylic acid copolymer	430 g
15	Polyethylene glycol	40 g
	Water purified	1890 g

Polish

20	Magnesium stearate	5 g
----	--------------------	-----

The dry ingredients given above were mixed well in a mixer. Addition of granulation liquid was made and the mixture was kneaded and granulated to a proper consistency. The wet mass was pressed through an extruder and the granules
25 were converted to spherical form in a spheronizer. The pellets were dried and classified into suitable particle size ranges, e.g. 0.5-1.5 mm.

The polymer solution (I) was sprayed on the uncoated pellets in a fluidized bed apparatus under conditions suitable for the equipment used.

30

The polymer dispersion (II) was sprayed on the subcoated pellets in a fluidized bed apparatus. The enteric-coated pellets were classified, polishing material was

admixed and the pellets were filled into hard gelatin capsules in an amount corresponding to 20 mg of omeprazole, using a capsule filling machine.

Biopharmaceutical tests.

5

The enteric coated formulations according to Example 2 have been tested in humans with good results.

CLAIMS

1. An oral enteric coated formulation containing a core material of an active substance coated with one or more subcoating layers and one or more enteric coating layers characterized in that the core material as active substance contains a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 % as determined by X-ray powder diffraction and optionally an alkaline reacting compound, on the core material applied subcoating layer(s), separating the core material from the enteric coating whereby the thickness of the enteric coating does not essentially influence the release of omeprazole into aqueous solutions at pH values predominantly present in the small intestine.
2. A formulation according to claim 1, wherein the formulation is a tablet formulation.
3. A formulation according to claim 1, wherein the formulation is a pellet formulation.
4. A formulation according to claim 1, wherein the enteric coating comprising an enteric coating material, optionally containing one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.
5. A formulation according to claim 4, wherein the enteric coating comprises water-based polymer solutions or dispersions of acrylates, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate and/or cellulose acetate phthalate.
6. A formulation according to claim 1, wherein the enteric coating constitutes from 1.0 % by weight of the weight of the core material.

7. A formulation according to claim 6, wherein the enteric coating constitutes at least 3.0 % by weight of the weight of the core material.
8. A formulation according to claim 1 wherein the subcoating layer(s) comprise
5 polymeric, filmforming compounds or tablet excipients which are soluble or insoluble but disintegrating in water, and optionally containing pH-buffering, alkaline compounds.
9. A formulation according to claim 1 wherein the produced enteric coated
10 formulation contains an overcoat, optionally comprising one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.
10. A process for the manufacture of a formulation according to claim 1 in which the core material containing magnesium omeprazole optionally mixed with an
15 alkaline reacting compound is coated with one or more subcoating layers, whereafter the subcoated core material is further coated with one or more enteric coating layers.
11. A process according to claim 10, wherein the subcoating layer(s) is applied
20 on the core material by a drycoating process.
12. An oral enteric coated formulation according to any of claims 1 to 9 for use in therapy.
13. An oral enteric coated formulation according to any of claims 1 to 9 for use
25 in inhibiting gastric acid secretion in mammals and man.
14. An oral enteric coated formulation according to any of claims 1 to 9 for use in the treatment of gastric acid related diseases in mammals and man.

15. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals and man.
- 5 16. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for treatment of gastric acid related diseases in mammals and man.
- 10 17. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.
- 15 18. A method for the treatment of gastric acid related diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00681

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/24, A61K 9/52, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0342522 (EISAI CO., LTD.), 23 November 1989 (23.11.89), page 2, line 34 - page 3, line 29, claims --	1-16
X	EP, A2, 0247983 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 5, line 6 - page 9, line 12, claims --	1-16
A	EP, A2, 0124495 (AKTIEBOLAGET HÄSSLE), 7 November 1984 (07.11.84) -----	1-16

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 October 1994

Date of mailing of the international search report

25 -10- 1994

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00681

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:
Methods for treatment of the human or animal body by surgery or therapy,
as well as diagnostic methods (see PCT Rule 39(iv)).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/10/94

International application No.
PCT/SE 94/00681

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0342522	23/11/89	SE-T3- 0342522 DE-U- 6890056 ES-T- 2051919 JP-A- 1290628 US-A- 5035899	30/01/92 01/07/94 22/11/89 30/07/91
EP-A2- 0247983	02/12/87	SE-T3- 0247983 AU-B- 601974 AU-A- 7191287 CA-A- 1292693 DE-A- 3783394 EP-A- 0496437 EP-A- 0567201 ES-T- 2006457 GB-A- 2189698 JP-A- 5294831 JP-A- 62258320 NO-B- 174239 US-A- 4786505	27/09/90 05/11/87 03/12/91 18/02/93 29/07/92 27/10/93 01/01/94 04/11/87 09/11/93 10/11/87 27/12/93 22/11/88
EP-A2- 0124495	07/11/84	SE-T3- 0124495 AU-B- 563842 AU-A- 2525784 CA-A- 1264751 GB-A,B- 2137616 JP-C- 1651336 JP-B- 3013233 JP-A- 59167587 SU-A- 1314953 US-A- 4738974	23/07/87 06/09/84 23/01/90 10/10/84 30/03/92 22/02/91 21/09/84 30/05/87 19/04/88